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ASSESSMENT OF RISK FROM LOW DOSES: Contribution of Epidemiology

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When the cause of disease is a stochastic process, exposure to it may increase the risk in linear proportion to the amount of exposure down to vanishingly low doses, unless there is some biological mechanism that prevents or eliminates the effect. Epidemiology cannot determine whether or not an effect is produced at very low doses. What it can do is to (i) provide quantitative evidence of an effect at lower doses than is generally possible in the laboratory, (ii) check that postulated biological models have not underestimated the effect at low doses, and (iii) indicate the relative susceptibility of laboratory animals and humans. Observations on humans exposed to ionizing radiation and tobacco smoke provide examples of all three uses.

Keywords: low dose risks; epidemiology; ionizing radiation; tobacco smoke.

INTRODUCTION

The assessment of risk from low doses is exceptionally difficult. Like Thurber, who tossed and turned in bed worrying over a problem for many minutes, which was all he could manage without falling asleep, I have worried over how I could introduce this discussion in a simple and arresting way. I gave up, however, because I could not construct an appropriate sentence without mentioning cause, and this, unqualified, would be liable to be misunderstood. For I should have to use 'cause' in its epidemiological sense of an agent that is associated with a disease in such a way that, over a wide range of exposures, increased exposure to it is associated with an increased risk and decreased exposure with a decreased risk.

The difficulty with the assessment of the effect of low doses arises when the cause of disease, so defined, exerts its effect by means of a stochastic process. This implies, other things being equal, that with low doses the risk produced will be linearly proportional to the amount of exposure down to near zero. Such processes, it seems, are responsible for the production of cancer, of genetic mutations leading to hereditary disease, and of some congenital anomalies, including perhaps some types of impaired intelligence, and for these conditions we are constantly faced with the problem of deciding whether linearity continues to hold at very low levels or whether there is some biological mechanism—for example, an error-free repair mechanism or a stress reaction—that modifies or even eliminates the effect.

What Epidemiology Can Do

Epidemiology cannot solve this problem, but it can do three things. Firstly, it can provide quantitative evidence to test the validity of any proposed biological model at moderate doses: that is, doses that may increase the risk of a common disease by, say, 20 to 100%. Such doses are often much smaller than can be tested in the laboratory, because epidemiological observations can be made on much larger numbers of people in society than of animals in the laboratory. Secondly, epidemiology can check that at lower levels the postulated biological model has not substantially underestimated the risk. Thirdly, and most importantly, it can demonstrate the relative susceptibility of laboratory animals and humans; for without some epidemiological evidence, any quantitative extrapolation from animal experiments can be only guesswork, even if humans and the laboratory animals can be shown to react to the cause and absorb, metabolize, and excrete it in similar ways.

In this paper, I shall provide some examples of these contributions and their statistical and logical limitations, using data relating to the two causes of disease for which we have the largest amount of quantitative data: namely, ionizing radiation and tobacco smoke.

IONIZING RADIATION

Model for Carcinogenesis

One of the finest sets of quantitative epidemiological data that has ever been obtained is that obtained by the Life Span study of 80,000 survivors of the Hiroshima and Nagasaki explosions[1,2]. This has provided cancer incidence and mortality data that can be related to doses of radiation estimated separately for each individual, as a result of a detailed study of his or her precise location and potential shielding at the time of the explosions, combined with the results of experimental explosions. The latest findings[3,4], based on nearly 9000 cases, of which some 600 were caused by the radiation, provide strong support for a linear dose-response relationship for cancers other than leukaemia between 0.2 and 4 Sv. With exposures less than 0.2 Sv, the incidence is not significantly increased, but it is possible to test how well the

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data could be fitted with a linear quadratic relationship that would allow the risk at lower doses to be proportionately somewhat less than that extrapolated from higher doses, as *in vitro* experiments suggest is likely to be the case. With adjustment for dosimetry errors, which it is estimated may be as much as 35%[5], the maximum likelihood estimate of the low dose reduction factor for cancers other than leukaemia (that is, the factor by which the risk coefficient extrapolated from a linear relationship can be divided to give the risk coefficient for doses below 0.2 Sv) is 1.05 with a 90% confidence interval of 0.6 to 1.6. For leukaemia (other than chronic lymphatic leukaemia, which is not caused by radiation) the estimate of the reduction factor is 2.5, significantly greater than that for other cancers, with a 90% confidence interval of 1.3 to 8.4[6].

Validity of Model for Low Doses

That a model that leads to a linear relationship with a reduction factor of about two for low doses does not materially underestimate the risk can be tested, in the case of ionizing radiation, by observation of the mortality of radiation workers and, in respect of leukaemia, by the incidence of the disease in young people in parts of the world that have had unusual amounts of fallout from the testing of nuclear weapons and have had reliable cancer registration data dating back before the maximum fallout occurred.

Observations on a sufficiently large number of workers for any likely excess to be detected have recently been reported by a study group of the International Agency for Research on Cancer[7] which has brought together, in a comparable way, observations on nearly 100,000 radiation workers (over 80% male) in Canada, the US and the UK over periods up to 42 years. The workers received a dose of 40 mSv on average (male workers 46 mSv) but the dose distribution was very skewed, 60% receiving less than 10 mSv and less than 2% more than 400 mSv. The results, expressed in terms of excess relative risks per Sv, are summarized in Table 1. For leukaemia, the regression coefficient of the excess relative risk was 2.18 Sv^{-1} with a 90% confidence interval of 0.1 to 5.7 Sv^{-1}. This is intermediate between the best estimates for male atomic bomb survivors exposed between 20 and 60 years of age, as derived by the International Agency for Research on Cancer using a linear model, and the preferred linear-quadratic model. For fatal cancers other than leukaemia there was no excess, but the 90% confidence limits of the regression coefficient comfortably embraced that for men exposed to the atomic bombs at similar ages, on the assumption of a linear relationship with dose over the range of 1 mSv to 4 Sv, and even more comfortably if some reduction factor for low doses is allowed.

Table 1. Excess relative risk in nuclear industry workers compared with atomic bomb survivors: men only (after Cardis *et al.*[7])

Population	All cancers excluding leukaemia: [a]ERR per Sv	90% confidence interval	Leukaemia excluding CLL: [a]ERR per Sv	90% confidence interval
[b]Nuclear industry workers	−0.07	(−0.29, 0.30)	2.18	(0.13, 5.7)
[c]Atomic bomb survivors:				
linear	0.18	(0.05, 0.34)	3.67	(2.0, 6.5)
linear quadratic	NA		1.42	(<0, 6.5)

[a]Excess relative risk (ERR) estimated for organ dose (bomb survivors) and for 1 cm depth dose (nuclear workers)
[b]Adjusted for age, socioeconomic status, facility, and calendar time
[c]Derived by authors from Japanese data for men exposed at ages 20–59 years, restricted to subjects with kerma dose less than 4 Gy and age under 75 years

Similar observations on the effects of fallout in large populations have been obtained in two studies. In one, the incidence of leukaemia was examined in Utah, the area most exposed to fallout from the weapon testing in Nevada in the early 1950s[8]. In the 10 years following exposure, a significant excess ($p < 0.02$) was found in young people under 20 years of age exposed to red marrow doses estimated to have been between 3 and 26 mGy, depending on their place of residence. This led to an estimate of risk about twice that predicted from the Japanese experience, but not significantly different from it. The other set of data, the incidence of leukaemia in children under 15 years of age in the five Nordic countries over the period 1948 to 1987[9], showed a slight excess in the 7 years following exposure in those who were exposed to high levels of fallout (averaging 0.3 mGy a year to the bone marrow for up to 4 years) compared to children who experienced only medium exposures (averaging 0.1 mGy a year). This led to an estimate of risk that was just statistically significant ($p = 0.05$) and again about twice that predicted from the Japanese data, but not significantly different from it.

These three sets of observations extend the evidence for a leukaemogenic effect down from 200 to about 1 mGy and give some support to the concept of extrapolating from higher doses using a linear-quadratic model. The one set that provides data for other fatal cancers serves only to show that linear extrapolation dose not cause the risk to be substantially underestimated.

Species Differences in Susceptibility

These observations have not been used to examine differences in susceptibility between humans and laboratory animals, presumably because direct observations on humans were already becoming available when the need for determining the risk at low doses came to be felt. The same was not true, however, for genetic mutations, as the only observations that seemed likely to be available for many years, when the need for them was felt, were those for laboratory animals and plants. These led the Medical Research Council to conclude in 1956 that the dose required to double the normal incidence of genetic mutations was 0.3 to 0.8 Gy[10]. Since then, observations have been made on the prevalence of congenital anomalies, the sex ratio at birth, stillbirth and neonatal death rates, birth weight, and anthropometric measurements in infancy for all children born in the two bombed cities and have subsequently been extended to include studies of cancer incidence, cytogenetic changes, and mutations altering the electrophoretic mobility or

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activity of 30 proteins. They are now being extended further to include studies of constellations of lymphocytoid cell lines from irradiated and control parents and their children.

By 1990, no statistically significant effects had been seen with any of eight indicators. The regressions on dose for six of them are shown in Table 2. For three of them the direction of the trend is *contrary* to what would be expected from damage to parental germ cells. The other two indicators cannot be easily summarized in the same way. One—balanced structural rearrangement of chromosomes—was seen *less* often in children of exposed parents than in children of controls. The other—the frequency of *de novo* protein mutants—has so far been one in each group[11]. Not all these indicators have an equal contribution from spontaneous mutations and Neel *et al.* calculate that the most probable dose of acute low LET radiation required to double the mutation rate is between 1.7 and 2.2 Gy[12]. For low dose rate exposures, mouse experiments suggest that the effect should be halved, leading to a doubling dose of the order of 4 Gy or *more*—five times the upper limit of the MRC's estimate based on studies of other species. Humans, it seems, are appreciably less susceptible to the induction of genetic mutations by ionizing radiation than was originally estimated from experiments on laboratory animals.

TOBACCO SMOKE

Dose Response Relationship

Tobacco smoke is a complex agent containing some 4000 identified chemicals, but the observations of its quantitative effect are nevertheless of some general scientific as well as public health, interest. Case-control and cohort studies have both suggested that for lung cancer—for which cigarette smoking has been principally responsible in all developed countries, causing up to 95% of cases in men—the risk is linearly proportional to the number of cigarettes smoked per day, down to the lowest level observed in regular cigarette smokers: namely, one to four a day. One could hardly expect to see a much better fit to a linear relationship in any biological experiment than the mortality rates observed in cohorts of British doctors who said they were smoking different amounts[13]. Yet the conclusion that there is such a relationship is almost certainly wrong; for the determination of an individual's exposure by his response to a question about the number of cigarettes smoked per day is too inaccurate. Even if we leave aside the problem of the distribution of the smoke droplets on the bronchial mucosa, there is the fact that the amount smoked per day, though often remarkably constant over many years, does change with time. In our study, it so happened that we had information about the amount individuals smoked on several occasions and we were, therefore, able to examine the relationship after eliminating men who reported differences in consumption of more than five cigarettes a day on different occasions[13]. The dose-response relationship was then better fitted by a quadratic relationship. The reason for the difference is easy to understand, for when only the last report of the amount smoked is taken into consideration the group of very light smokers will include some men who used to smoke more but have reduced their smoking, which will have inflated the risk, while the group of very heavy smokers will include some men who used to smoke less but have increased their smoking, which will have reduced the risk. The observations on cigarette smokers provide a particularly glaring example of the way errors in the measurement of exposure distort the observed dose-response relationship, but the effect is of relevance to many other situations: namely, that errors in the assessment of measurement will not only diminish the regression of risk on recorded dose but will also tend to make a higher powered relationship appear linear.

Table 2. Regression on parental dose of six indicators of genetic damage (after Neel *et al.*[12]).

Indicator	Regression on dose (Sv) ± standard error
Untoward pregnancy outcome	.00264 ± .00277
Mortality from non-malignant disease	.00075 ± .00154
Incidence of cancer under 20 years	−.00038 ± .00028
(most genetic subset)	−.00005 ± .00015
Sex chromosome aneuploidy	.00044 ± .0009
Mutation altering serum or blood protein	−.00001 ± .00001
Offspring malness (mothers only)	.0027† ± .0040

† Genetic theory predicts a decrease in rate

Effect of Environmental Smoke

In the case of tobacco smoke this finding, that the risk of lung cancer may be proportional to the square of the number of cigarettes smoked per day rather than to the number itself, makes good sense, as tobacco smoke has both initiating and promoting qualities. It also has obvious implications for the estimate of the effect of environmental tobacco smoke. Eleven years ago, when environmental tobacco smoke was more common than it is today, Jarvis *et al.* estimated from blood levels of cotinine, a metabolite of nicotine with a relatively long biological half-life, that the average so-called 'passive smoker' inhaled each day smoke equivalent to about one tenth of a cigarette, as smoked by an active smoker[14]. The life-time risk of environmental smoke, as estimated by extrapolation from the quadratic relationship observed in active smokers, would then be very small[15]—about 10% of that in non-smokers and substantially less than the 50% estimated from the case-control studies in which the risk of non-smokers married to smokers is compared with that of non-smokers married to non-smokers[16].

The conclusion drawn by extrapolation from the results observed in active smokers was of some importance as it was argued by apologists for smoking that the risk estimated from case-control studies was biased by errors in the smoking history of non-smokers, self-reported non-smokers married to smokers being postulated (not unreasonably) to have included a higher proportion of people who had smoked to some extent in the past than those married to non-smokers. I doubt, however, if extrapolation from the experience of active smokers is justified; not because of doubt about the nature of the dose-response relationship in active smokers, but because the physical and biochemical

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differences between active and passive smoking are too great. Exhaled smoke not only undergoes chemical and physical changes in the atmosphere, but it is inhaled by passive smokers more deeply than by active smokers. It cannot, therefore, be assumed that the carcinogenic effect on the bronchi, which is dependent on the deposition of tar droplets on the bronchial mucosa, bears the same proportion to the blood cotinine level in passive smokers as in active smokers. The only way we can assess the effect of passive smoking is by case-control or cohort studies of passive smokers themselves. As the risk is certainly very small this, in effect, means by case-control studies. Dr Coggon discusses the hazards of bias and confounding in case-control studies elsewhere in this issue[17], and I will, therefore, say only that in this case confounding is unlikely to be a problem, that Wald *et al.* have shown that recall bias cannot be quantitatively sufficient to account for the findings[16], and that a reasonable estimate of the effect of environmental smoke is that it may have caused a quarter of the lung cancers in non-smokers.

CONCLUSIONS

Epidemiological observations are, I conclude, an essential part of our armoury against both environmental hazards and socially disruptive controls. It may not often be possible to obtain direct estimates of risk down to such low doses as those I have discussed, but some quantitative estimates based on human data (given that the exposures have already occurred) are a necessary complement to laboratory evidence at levels below those that give rise to acute toxicity, if sensible decisions are to be reached.

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